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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,872	11/28/2000	Gyula Hadlaczky	24601-402F	8394

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EXAMINER	
HELMER, GEORGIA L	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,872	HADLACZKY ET AL.	
	Examiner	Art Unit	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,7,9-27,29-32 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,7,9-27,29-32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *14May03, 30June05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 June 2005 has been entered.

1. Claims 1, 4, 6, 7, 9 - 27, 29–32 and 34 are pending and are examined in the instant action.

2. All rejections not addressed below have been withdrawn.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement.

4. Applicant's IDSs dated 30 June 2005 and 22 May 2003 are acknowledged and signed copies are included with this action.

Claim Rejections - 35 USC § 112 Written Description

5. Claims 1, 4, 6, 7, 9 - 27, 29–32 and 34 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record on pages 3-5 of the Office Action of 30 September 2003.

Applicant's arguments filed 30 June 2005 have been fully considered but are not deemed persuasive.

Applicant traverses asserting the specification provides detailed definitions and structural characterizations of a SATAC and each of its elements, so that it is clear that Applicant was in possession of a SATAC as of the filing date of the instant application and as of its earliest priority date. Applicant further says the specification describes how plant artificial chromosomes differ from other artificial chromosomes (Response, p. 12): "a mammalian artificial chromosome (MAC) is a piece of DNA that can stably replicate and segregate alongside endogenous chromosomes. It has the capacity to accommodate and express heterologous genes inserted therein. It is referred to as a mammalian artificial chromosome because it includes an active mammalian centromere. Plant artificial chromosomes...refer to chromosomes that include plant...centromeres" (specification, p. 16).

Applicant's traversal is unpersuasive. Applicant defines the artificial chromosome as being a piece of DNA having certain qualities. However Applicant's definition and description is given in terms of "chromosomes". Chromosomes consist of nucleic acids and proteins, the proteins being histone proteins as well as non-histone proteins, not naked DNA. It would appear that Applicant's description of artificial chromosome, as DNA, is lacking at least one family of components—the proteins. Furthermore,

describing an artificial chromosome as DNA that can stably replicate and segregate alongside endogenous chromosomes, and having the capacity to accommodate and express heterologous genes inserted therein, fails to distinguish artificial chromosomes from "wild-type" chromosomes. "Wild-type" chromosomes can stably replicate and segregate alongside endogenous chromosomes, and have the capacity to accommodate and express heterologous genes inserted therein, as is known from the literature, which abounds with examples of transgenic animals, fungi and plants, and many progeny generations of these transgenics.

Applicant traverses primarily that the instant Application provides exemplary SATACs evidencing Applicant's possession of the claimed subject matter.(Response of 30 June 2005, p.11-12). Applicant says that the specification describes the generation of animal cell lines such as G3D5 and HID3 containing megachromosomes (exemplary SATACs), and that these cells lines have been deposited in the ECACC and gives accession numbers. Applicant's argument is unpersuasive. Overcoming a written description rejection under 112.1 cannot be overcome by deposit of biological material unrelated to the instant claims. The instant claims are drawn to plant-functional SATACs, which differ from the deposited animal SATACs in at least the presence of a plant centromere, as admitted by Applicant on p. 16 of the specification.

Applicant further asserts that the specification depicts the structures of SATACs schematically in Figures 2 and 3 of the specification. Applicant's assertation is unpersuasive. Figures 2 and 3 show a schematic of a complex macromolecular pathway starting with mouse chromosome #7 being transfected with foreign DNA, which

DNA is described as specific λ DNA. The other components are macromolecular complexes, comprising for example heterochromatin and euchromatin.

Applicant, noting that the instant Application is a CIP of US 6,077,697, which contains issued claims directed to methods of producing and isolating SATAC as well as composition claims directed to isolated SATACs, asserts that therefore these provide SATACs and their structural elements. Applicant asserts the issued patents and the instant case are related as CIP's of a common parent and thus Applicant has demonstrated possession of SATACs as of the earliest filing date (Response of 30 June 2005, p. 12-13). Applicant's traversal is unpersuasive. First, only one of the patented claims is drawn to plant-functional SATACs, as instantly claimed. Second, this Office Action has been reviewed by a PTO Director.

Applicant fails to provide Written Description with respect to the structural and physical characteristics of the claimed invention. There is no structural description, other than saying that a SATAC is a piece of DNA, of what comprises a SATAC, particularly a plant-functional SATAC. Applicant fails to mention or describe in any way, other required components, namely the proteins. Therefore Applicant is claiming a genus of macromolecular components, yet there is no description to the structural features that define the genus, as required by Lilly, cited previously.

Claim Rejections - 35 USC § 112.1 Enablement

6. Claims 1, 4, 6, 7, 9 - 27, 29 – 32, and 34 remain rejected under 35 U.S.C. 112, first paragraph, for reasons of record .

This rejection is repeated in part for reasons of record as set forth in the Office Actions mailed 30 September 2003 (pages 5-7) and 21 June 2004. Furthermore, the Examiner now relies upon Ohgawara et. al. (1983) and Potrykus (1990) to demonstrate the unpredictability inherent in liposome-mediated plant transformation (claims 9 and 10); and in plant transformation and maintenance of the exogenous DNA in plants as generally claimed, particularly in monocots including rice, maize or rye (claims 29 and 30).

Ohgawara, et. al., (1983) studying liposome-encapsulating plasmid DNA by plant protoplasts and the molecular fate of foreign DNA, found variations in DNA uptake among protoplasts from different plant species (p. 145 Abstract). In fact, after one week in culture, in only one plant, D. carota (carrot) was even a trace amount of plasmid DNA detected (p. 147, column 2, top ¶).

Potrykus (1990), reviewing gene transfer to cereal plants (monocots), teaches the general recalcitrance of monocots to transformation; and discusses the variability relating to gene transfer, considering the biology of gene transfer, saying that a transgenic plant can only result from integrative transformation in a totipotent cell or a cell that has a clonal connection to the "germline". Issues of concern here are (1) Not all plant cells are totipotent. (2) Plant cells differ in their capacity to respond to triggers, a phenomenon termed *competence.* (3) Cells from which it is hoped to regenerate transgenic plants must be competent for both regeneration (in a broad sense) and integrative transformation. (4) Plant tissues are composed of cells competent for many different responses. Considering the two states of competence essential for recovery of

transgenic plants the following situation has to be considered: a/ A very small minority of cells in plant tissues will be competent for both transformation and regeneration. b/ Others will be competent for transformation or regeneration. c/ A large fraction of the cell population will be potentially competent, meaning that given the correct treatment they will have the potential to shift to the competent state. d/ A variable proportion of cells will not even be potentially competent, but will be non-competent. (5) The relative composition of cell population in tissues is determined by the genotype, the type of organ, the developmental state of the organ, and even the individual history of the experimental plant (p. 538, column 1, bottom ¶).

Of 23 different plant transformation techniques, only two, direct gene transfer into protoplasts and microprojectile bombardment, have shown any promise in either producing transformed monocot cells, whole transformed monocot plants, or transformed offspring (see pages 536-537). As the claims broadly read on any transformed plant of any of a multitude of unrelated species; and since particularly claims 29 and 30 read on a multitude of recalcitrant monocotyledonous species; the specification does not provide any teachings of plant transformation of any species, which would be required to overcome the evidence of unpredictability inherent in obtaining transformed plant cells as claimed.

Microinjection (as claimed in claims 9 and 10) uses microscopic devices to deliver DNA to defined cells in such a way that the infected cell survives and proliferates. Transfer to structures of more than one cell can only produce transgenic chimeras, and transgenic offspring can only be expected if the transgenic sector

contributes to the floral meristems, so that no transgenic offspring have been produced (p. 541, column 1, middle ¶).

Applicant's arguments filed 30 June 2005 have been fully considered but are not deemed persuasive. Applicant largely refers to the Fabijanski declaration of 03 March 2004.

The declaration of Fabijanski dated 30 March 2004 has been carefully considered and is unpersuasive.

The Declaration states that

> "using methods and materials described in the application and standard methods as described herein, myself and other scientists involved in these projects have demonstrated that satellite artificial chromosomes can be transferred to plant protoplasts using either (a) micro-cell mediated fusion of SATAC containing murine cells with plant protoplasts or (b) lipid-mediated transfection of isolated SATACs into plant protoplasts. Further we have demonstrated that plant artificial chromosomes can be generated by introduction of heterologous DNA into plant cells and growth under selective conditions to produce cells containing plant SATACs. As exemplified by the results shown below we have demonstrated element-for-element and step-for-step that, by following the teachings in the application, a SATAC can be introduced into a plant cell. In addition, as exemplified by the results shown below, we have demonstrated element-for-element and step-for-step that, by following the teachings in the application , plant artificial chromosome can be generated by i) introducing a DNA fragment with a selectable marker into a plant cell; ii) growing the cell under selective conditions to produce plant cells that have incorporated the DNA into their genomic DNA such that a plant satellite artificial chromosome is produced; and iii) selecting a cell that contains a plant satellite artificial chromosome. (Declaration, p. 2)

The Declaration describes transfer of a mouse SATAC into plant protoplasts using microcell-mediated fusion of mouse microcells with tobacco protoplasts (Declaration , p. 3), microcell-mediated fusion of mouse microcells with Arabidopsis thaliana protoplasts (Declaration, p. 4) and cationic lipid-mediated transfection of mouse artificial chromosomes with rice protoplasts (Declaration, p.5).

The Declaration indicates "generation of plant artificial chromosomes (Plant SATACs)" by the following steps (Declaration pages 5-6):

(1) construction of heterologous DNAs—

(a) Vector pAgIIa, a vector containing a 334 bp region of homology to tobacco pericentric DNA,(the central AT-rich region of a tobacco rDNA intergenic spacer capable of amplification) as well as a detection marker containing mouse satellite DNA , and (b) a second DNA, the "targeting DNA" containing a region of homology to pericentric DNA sequences (a 1.7 Kb portion of the 26S rDNA coding region);

(2) introduction of the DNAs into plant cells and selection—

(c) by introduction of Vector pAgIIa DNA and "targeting DNA" into tobacco protoplasts using transfection, followed by culture of plant tissue microcalli under selective antibiotic conditions;

(3) Identification of amplified DNA molecules;

(4) Generation of microcalli from the protoplasts containing the amplified DNA molecules by selective growth of the cells on the selection agent hygromycin (Declaration p 6., final 2 ¶s through 1st ¶ of p. 7).

The Declaration of Fabijanski provides information of the production of a plant SATAC, and the production of transgenic tobacco cells containing the plant SATAC. However the method of Fabijanski, as set forth in this Declaration, is not supported by the specification as of the earliest date of filing.

Fabijanski employs information and biological materials not available as of the earliest date of filing, namely April 1996. Fabijanski employs DNA sequences (Genebank X76056) not available until 27 September 1996 at the earliest. See Genebank accession number Y08422. Borisjuk et. al. (Plant Mol Biol 35, 655-660, 1997), provides information relating to the tobacco rDNA intergenic spacer regions capable of amplification and information relating to the homology to tobacco pericentric sequences, which Fabijanski used. This information was not publicly available before at least June 1997. Fabijanski required this information to do the experiments detailed in his Declaration.

Furthermore, the Fabijanski method employs in step 1 (Construction of heterologous DNAs) two different constructs: *Vector pAgIIa* containing a "sequence with homology to the pericentric DNA" and selectable markers, and a *targeting DNA* construct containing sequences with homology to the pericentric DNA sequences. Fabijanski uses two different defined sequences having specified properties for this purpose, as discussed above. One of the DNA sequence used is small (334 bp) and

the other is larger (1.7 kb), suggesting that sequence size may be an important consideration. Are these sequences with "homology to the pericentric DNA" interchangeable? The DNA sequences used have specific characteristics, such as homology to pericentric DNA, which recommended their use in the method of Fabijanski. Why are these sequences used preferentially in this example?

The specification describes (p. 42-48) in vitro construction of artificial chromosomes, whereby the artificial chromosome can be constructed by assembling the structural and functional elements that contribute to a complete chromosome capable of stable replication and segregation alongside endogenous chromosomes, and physically ligating the appropriate components. These elements include identification and isolation of components of the artificial chromosome starting with animal cell lines on deposit (p. 43). The elements enumerated are centromeres (p. 44-45), telomeres, megatreplications, filler heterochromatin and selectable markers (p. 46-47). Surely this method taught by the specification, and involving animal chromosomes, is not the method of Fabijanski as set forth in the Fabijanski Declaration.

Furthermore, the mere germ of an idea does not constitute an enabling disclosure, and the specification, not the knowledge of one skilled in the art must supply the enabling aspects of the invention. See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2nd 1001, 1005 (Fed. Cir. 1997).

See also In re Glass, 181 USPQ 31, 34 (CCPA 1974), which teaches that references published after the filing date of an application may not be relied upon for the enablement of the specification.

The specification as filed gives no information or guidance for obtaining a plant origin of replication or a plant centromere(s) (see claim 34) which would function as desired to produce a transgenic plant transgenic for an artificial chromosome. Undue experimentation would be required to determine what DNA sequence(s) would function as desired in the claimed invention. What DNA sequence containing homology to what DNA would be appropriate as pericentric DNA? Applicant must provide sufficient guidance to address these issues and those above. Without such guidance the experimentation required would not be routine, but would be undue. This would impose a burden on the skilled artisan, without a reasonable expectation of success.

Applicant is not enabled for the claimed invention as commensurate in scope with the claims. The claims are broadly drawn to methods of making and using satellite artificial chromosomes for host cells, including yeast, animal and plant hosts, and wherein the satellite artificial chromosomes are yeast, animal and plant satellite artificial chromosomes.

Applicant traverses saying primarily (Response of 30 June 2005, p. 16-20) that the working examples are exemplified in mammalian cells, and the Applicant asserts that these methods are applicable to any plant and animal cell type and any plant or animal species of SATAC. Applicant's traversal is unpersuasive, as discussed previously. Applicant's assertions, that plant and animal SATACs and hosts transformed therewith are the same, are refuted by the evidence provided by the Examiner in the original enablement rejection of the Office Action of 7 November 2002, p. 5-9); the newly cited Ohgawara et. al. and Potrykus references demonstrating the unpredictability inherent in

the introduction and maintenance of heterologous DNA into plant cells and whole plants; and the reliance of the Fabijanski Declaration on much information, including plant DNA molecules and plant transformation techniques, not disclosed by the specification or present in the deposited cell lines, and not available as of the earliest date of filing.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 11 of the instant case is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,077,697. The conflicting claims are coextensive. It would have been obvious to one of ordinary skill in the art to utilize the method of producing a SATAC via introducing "one or more" DNA fragments into a cell, as claimed in the patent; to obtain the method of producing a SATAC via introducing "a" single DNA fragment into a cell, as instantly claimed.

Applicant argues that the obviousness-type double patenting rejection of 21 June 2004 is improper, since it was actually a statutory double patenting rejection, and therefore a new ground of rejection (Response, p. 20-21).

The Examiner notes that the identical rejection was made in the Office Action of 30 September 2003 (see ¶ bridging p. 16-17). Therefore, Applicant's assertion, that the final Office Action instituted a new ground of rejection, is incorrect. However, the Examiner concedes that the prior two rejections were confusing in their statement that the claims were "identical". The Examiner has clarified the explanation, and thanks the Applicant for bringing this to our attention.

Remarks

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 571-272-0796. The examiner can normally be reached on Monday -Thursday, 10:30 am - 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Art unit 1638 – Transgenic Plants
14 September 2005

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